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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/572,905	COMBARET ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10 and 12-17* is/are pending in the application.

4a) Of the above claim(s) *16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10, 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/22/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Attached alignment of claimed sequences to WO02/097093.

DETAILED ACTION

1. This action is in response to papers filed 11/23/2009.

2. Claims 10, 12-17 are pending. Claims 1-9 and 11 have been cancelled.

3. Claims 16-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12/08/2007.

4. Claims 10 and 12-15 are rejected. The rejections are presented below and have been altered to reflect amendments to the claims. Specifically the amendment to the claim to specify the patient is human. Response to arguments follows

5. This action is FINAL.

Claim Rejections - 35 USC § 112/Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 10 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement

requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Breadth of the claims

Claim 10 is drawn to a method for determining a good or poor prognosis for a patient suffering from neuroblastoma comprising extracting biological material from a tumor or bone marrow sample, contacting the sample with a combination of 9 to 37 target genes comprising SEQ ID No. 2, 3, 7, 8, 10, 22, 25, 29, and 34, and determining cluster analysis of the target genes to determine whether the patient has a good or poor prognosis wherein a patient previously clinically classified as good prognosis is a patient diagnosed with a stage 1,2, or 4s neuroblastoma and did not die within 75 months of diagnosis and a patient previous clinically classified as poor prognosis is a patient diagnosed with a stage 4 neuroblastoma or died within a 75 months of diagnosis. Claim 12 define the biological sample as any sample taken from any patient. Claims 13-15 define the support and the reagent.

The claims are drawn, therefore, to determination in any human patient good or poor prognosis by determining the expression of 9 to 37 genes compared to patients previously clinically classified as good or poor prognosis.

Nature of the Invention

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Teachings in the Specification and working examples

The specification discloses that there are 6 stages of neuroblastma (stage 1, 2a, 2b, 3, 4, and 4S (p. 2 lines 10-25). The specification asserts that prognosis of neuroblastoma can be determined by analyzing the expression of target genes selected from 37 genes in Table 1 which are expressed differentially depending on whether the patient has good or poor prognosis (p. 3 lines 20-26).

Figures 1-5 asserts association of 23 samples of tumors derived from patients with good prognosis or poor prognosis and probe sets from the genes presented in Table 1 (p. 22-23). However the figures do not show which probe sets are correlative to good or poor prognosis.

23 neuroblastoma samples were collected from patients who were 10.5 months old (p. 23 lines 10-15). 12 samples were in stage 1 or 2, 4 in stage 4s and 7 in stage 4 (p. 23 lines 15-18). Therefore no stage 3 tumors were evaluated.

The specification asserts that patients who died during the study and patients with a stage 4 neuroblastoma or patients who died during a period of 75 months were described as patients with poor prognosis (p. 23 lines 23-25). The specification asserts that patients alive and having developed a stage 1, 2, and 4s neuroblastma were

describes as patients with good prognosis (p. 23 lines 23-25). The specification asserts that the analysis was carried out on 8 poor prognosis patients and 15 good prognosis patients (p. 23 lines 27-28).

The specification discloses that total RNA was extracted (p. 23 line 30) and cDNA was synthesized (p. 24). The specification discloses that expression of approximately 10000 genes was analyzed between good prognosis and poor prognosis patients using the Affymetrix U95Av2 GeneChip (p. 25 lines 5-30).

The specification asserts that relevant genes which were correlated with a poor neuroblastoma prognosis were selected (p. 26 lines 28-30). The specification discloses a list of 37 genes which were differentially expressed in poor prognosis versus good prognosis samples (Table 2 p. 27-28). However, the claims are directed to 9 specific SEQ ID Numbers out of 37 potential genes which are associated to good or poor prognosis. The skilled artisan would have to perform undue experimentation in order to determine which other 28 genes are correlative to prognosis. This would require undue experimentation as each correlation must be directly examined with no guarantee of success of determining prognosis.

The specification discloses the simultaneous expression of the 37 genes of Table 2 in Figure 1 (p. 32 lines 10-25). The specification discloses the simultaneous expression of the 19 genes of Table 4 in Figure 2 (p. 34). The specification discloses the simultaneous expression of the 16 genes of Table 5 in Figure 3 (p. 35). The specification discloses the simultaneous expression of the 12 genes of Table 6 in Figure 4 (p. 36). The specification discloses the simultaneous expression of the 9 genes of

Table 7 in Figure 5 (p. 36). Therefore the specification seems to be asserting a correlation of the detection of over or underexpression of 9 genes to prognosis of neuroblastoma in a patient; however, the claims as broadly written encompass any expression level of the combination of sequences.

The instant specification asserts that there are 37 genes that are differentially expressed in good prognosis or poor prognosis patients (p. 27 lines 14-17). The instant specification discloses in table 2 specific Seq id numbers which are increased or decreased. However, this result in the instant specification can not be used as enabling support as the art teaches that such prognosis of neuroblastoma is unpredictable. Ohira et al.(see discussion below) teaches that prognosis depends on the age at diagnosis and the tumor stage. Schramm et al. teaches a similar screening method for prognosis using the same Affymetrix chip used by the instant specification but with no overlapping genes. Therefore Schramm et al. indicates that depending on the genes on the chip different associations are observed. Herein in the instant case depending on the 28 other genes which are tested the skilled artisan would have to determine an association with prognosis. The instant specification has not provided how many or which genes must be correlative in order to determine prognosis.

The claims are directed towards comparing the expression of the patient to known patient samples with stage 1,2, 4s or how did not die within 75 months of diagnosis for good prognosis or patients with stage 4 or who died within 75 months of diagnosis , however, the instant claims are towards a method for determining a good or poor prognosis in any patient. The instant specification has not provided an analysis in

which the skilled artisan is provided guidance as to which group a patient with stage 3 should be placed. Further, the claims seems to be differentiating a patient who did not die within 75 months of diagnosis and a patient who did die within 75 months of diagnosis into poor or good prognosis. Therefore the comparison data required patients to have been diagnosed with stage 1, 2, or 4s and did not die within 75 months of diagnosis. However the expression levels of the genes taken from the sample of the patient are performed at any time. The art (see discussion of Ohira et al) teaches that prognosis is dependent on the age of diagnosis, therefore poor and good prognosis would differ depending on the age of the patient and the stage at which the patient is diagnosed.

The American Heritage College dictionary defines prognosis as "a prediction of the probable course and outcome of a disease", "the likelihood of recovery from a disease"" or “a forecast or prediction”. In the instant case detecting and determining would be the same, with regard to the fact the skilled artisan would have to detect the expression levels and determine based on these expression levels rather the patient had good or poor prognosis. Herein in the instant case, the specification has not provided any guidance to determine the prediction, the probable course and outcome of a disease, the likelihood of recovery, or a forecast or prediction of the disease in the patient. Rather, the working example in the specification provides correlations of expression levels at particular stages of disease, guidance has not been provided as to how to extrapolate these expression levels to the prediction the probable course and outcome of a disease, the likelihood of recovery, or a forecast or prediction of the

disease in the patient. The art (Ohira et al) teaches that correlations of prognosis and expression of particular genes are unpredictable and require multiple testing. Further, the specification provides no guidance with regard to patient in stage 3. As such the instant specification has not provided guidance for the skilled artisan to determine good or poor prognosis based upon detection of expression of the claimed sequences.

The predictability or unpredictability of the art and degree of experimentation

Ohira et al. (Cancer Letters 2005 Vol. 228 p. 5) teaches that poor prognosis of neuroblastoma depends on age at diagnosis and advanced tumor stage (3 or 4) (p. 5 2nd column 1st full sentence). However, no stage 3 tumors were used in the instant study so therefore it is unknown if stage 3 tumors would have the same expression levels for each sequence. The claims are directed towards comparing the expression of the patient to known patient samples with stage 1,2, 4s or how did not die within 75 months of diagnosis for good prognosis or patients with stage 4 or who died within 75 months of diagnosis , however, the instant claims are towards a method for determining a good or poor prognosis in any patient. The instant specification has not provided an analysis in which the skilled artisan is provided guidance as to which group a patient with stage 3 should be placed.

The art teaches associations between expression studies and cancer prognosis are unpredictable and must be reproduced to determine if there is a correlation. Ohira et al. (Cancer Cell April 2005 Vol. 7 p. 337) teaches a method of predicting prognosis of

neuroblastoma using cDNA microarray (abstract). Ohira et al. teaches that gene expression analyses for cancer prognosis prediction should pay close attention to the reproducibility of obtained results (p. 345 1st column last paragraph). Ohira et al. teaches a complete cross validation analysis without introducing any information leakage and an independent test using new samples are necessary (p. 345 last paragraph). Therefore Ohira et al. exemplify that validation of initial screening results is essential. Here in the instant case it is not clear if any of this analysis was undertaken therefore it is unpredictable whether the results observed are adequate basis for a prognostic too.

Postfiling art, Schramm et al. (Clinical Cancer Research 2007 VOl. 13 p. 1459) teaches generating expression profiles of 47 neuroblastoma patients using Affymetrix U95A chip (abstract). Schramm et al. teaches a table of gene whose correlation was expressed and correlated to neuroblastoma outcome (table 2). Though Schramm et al. teaches the determination of prognosis in the same disease using the same microarray chip, the group of genes Schramm et al. asserts is predictive of prognosis does not overlap the genes asserted by the instant specification. Table 1 of the instant specification lists 37 target genes including SEQ ID No. 2,3, 7,8,10,22,25, 29 and 34 (p. 4 Table 1). The specification asserts that SEQ ID No. 2, 3, 7, 8, 25, and 34 are from genes whose function is known but which have never been related to neuroblastma (p. 5 lines 1-5). The specification asserts that SEQ ID No. 10, 29 are genes whose function is unknown (p. 5 lines 1-5). Therefore, even in the post filing art, the associations of the specific genes expression in the instant specification and prognosis of neuroblastma is

not observed in a method with similar steps using the same array. Therefore it is unpredictable that the gene expression associations observed in the instant specification are reproducible in any neuroblastoma tumor sample based upon the unpredictability in the art and post-filing art which does not observe the same gene associations.

Takita et al. (Genes, Chromosomes and Cancer 2004 Vol. 40 p. 120) teaches detection of early and late stage tumors using DNA microarray analysis. Takita et al. teaches that although 9 of the 13 early stage tumors and 4 of the 6 advanced stage tumors were classified as being in the same cluster the remaining tumors showed different expression profiles (abstract). Takita et al. teaches that both early and advanced stage tumors are heterogeneous in expression (abstract). Therefore Takita et al. teaches that tumor tissue in the same stage can have different expression profiles because of the heterogeneous nature of each tumor stage.

The state of the art teaches that there is a natural variation in gene expression among different individuals and the difficulty in applying gene expression results. The art of Cheung et al (Nature Genetics 2003 Vol. 33 p. 422) teaches that there is natural variation in gene expression among different individuals. Cheung et al teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data indicates that, for example, expression of *ACTG2* in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by

a factor of 2.4 or greater (Fig 3).

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of pathology 2001 Vol. 195 p. 53). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The prior art of Newton et al (Journal of Computational Biology 2001 Vol. 8 p. 37) further teaches the difficulty in applying gene expression results. Newton et al teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph).

Amount of Direction or Guidance Provided by the Specification

The specification does not provide guidance to correlate any type of poor or good prognosis by detection of expression of SEQ ID No. 2, 3, 7,8,10,22,25,29, or 34.

The art teaches that associations between gene expression and neuroblastoma is unpredictable and is not predictably reproducible.

The skilled artisan, therefore, would have to perform undue experimentation to

determine any prognosis of neuroblastma by detection of any level of expression of any of SEQ ID No. 2, 3, 7,8,10,22,25,29, or 34.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters, which would have to be studied prior to being able to practice the claimed invention as broadly as written.

The skilled artisan would have to determine the correlation of expression to any poor or good prognosis. The skilled artisan would have to reproducibly correlate any expression of any of SEQ ID No. 2, 3, 7, 8, 10, 22, 25, 29, or 34 to type of poor or good prognosis in any patient type.

The art teaches that there is a high degree of unpredictability in associations between expression and prognosis. Post-filing art teaches a different set of genes are correlative to prognosis even though Schramm et al used the same Affymetrix chip it his method.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed

invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification does not provide a predictable association of SEQ ID No. 2, 3, 7, 8, 10, 22, 25, 29, or 34 and determination of any poor or good prognosis of neuroblastoma. Further, the art teaches that such correlations are unpredictable and population specific.

Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Response to arguments

The reply traverses the rejection. A summary of the reply is presented below with response to arguments following.

(A) The reply asserts that the claims have been amended to human and therefore no longer are drawn to any patient (p. 4 A1).

This has been fully reviewed and has been found persuasive.

The issue with regard to any type of patient has been removed from the rejection above. However, this amendment is not sufficient to overcome the 35 USC 112/Enablement rejection presented above.

(B) The reply asserts that the claim has been amended to require a combination of 9 to 37 genes which includes at least SEQ ID no. 2, 3, 7,8, 10, 22, 25, 29, and 34 (p. 4 A2).

This has been fully reviewed but has not been found persuasive.

Although the claims have been amended, the claims still encompass detection of upregulation or downregulation of any number of genes which comprises 9 to 37 genes of the SEQ ID Nos. The specification has not provided which sequences need to be unregulated or down regulated and be predictive of poor or good prognosis. The claims assert that if the patient is clustered with the expression profile of patients with poor or good prognosis, than that patient is classified as poor or good prognosis. Herein in the instant case, though, the applicant appears to be attempting to limit the combination to only SEQ ID No. 2, 3, 7-8, 10, 22, 25, 29, and 34, however with the comprising language of step b, the combination of genes could be larger. Further, even if the claims are limited to the 9 genes it is still not clear how many of these Seq id number expression levels need to be the same as a particular poor or good prognosis group and be equated as such. For example, does the expression levels of all the Seq id numbers in a particular patient need to be the same as a patient with poor prognosis to be

equated as poor prognosis. Further, the American Heritage College dictionary defines prognosis as "a prediction of the probable course and outcome of a disease", "the likelihood of recovery from a disease"" or “a forecast or prediction”. In the instant case detecting and determining would be the same, with regard to the fact the skilled artisan would have to detect the expression levels and determine based on these expression levels rather the patient had good or poor prognosis. Herein in the instant case, the specification has not provided any guidance to determine the prediction, the probable course and outcome of a disease, the likelihood of recovery, or a forecast or prediction of the disease in the patient. Rather, the working example in the specification provides correlations of expression levels at particular stages of disease, guidance has not been provided as to how to extrapolate these expression levels to the prediction the probable course and outcome of a disease, the likelihood of recovery, or a forecast or prediction of the disease in the patient.

(C) The reply asserts that the claims only allow for two types of prognosis, good or poor (p. 5 B1). The reply asserts that the claims define the criteria for clinical classification and as such the patient’s expression profile will be clustered with either poor or good prognosis (p. 5 B1).

The reply asserts that Shannon et al. explains that in absence of formal statistical tests, external criteria are used to choose the number of clusters (p. 6 B1). The reply asserts that Shannon et al. states that although clustering has statistical pitfalls, this does not detract form the enablement of the claimed method (p. 6 B1).

The reply points to claim 10 showing the external criteria which defines the two groups of clusters and asserts that the fact that no expression profiles form stage 3 neuroblastoma patients were used to define the cluster is irrelevant (p. 6 B1). The reply asserts that if a sample from a patient clinically classified as having stage 3 is subjected to the method the sample will be clustered with either the good or poor prognosis group (p. 6 B1).

The reply asserts that Table provides the expression level for each gene as either under or over expressed on average in poor patients compared to good prognosis patients (p. 7 B1). The reply asserts that Table 2 identifies 13 genes with decreased expression and 24 with increased expression, however, the expression profile of a given patient is not going to necessarily fit the 13/24 score (p 7 B1).

This has been fully reviewed but has not been found persuasive.

Although the patient based upon the claim will only be clustered with good or poor prognosis, it is not clear which expression levels of the sequences must be the same in order to be classified as such.

The reply points to Shannon et al. to show that although there are pitfalls, the claimed method is enabled. Shannon et al. is drawn to a review of how to perform cluster analysis. Shannon et al teaches that "putative relationships between clusters of genes and phenotypes need to be recognized as nothing more than hypotheses generated by clustering methods. The clustering process has not statistically validated the relationships and they must be formally validated through additional experiments. (p. 48 1st column last full paragraph of Shannon et al.). Herein in the instant case, the

specification has not provided any evidence of testing the phenotype (e.g. prognosis of good or poor prognosis) with any population to determine if the 9 genes clustered can place a population into good or poor classifications.

The reply asserts that a given patient is not going to fit into a perfect score of 13/24, however, the reply has not provided any evidence as to how to determine which scores would be conclusive for determining that a patient have a poor prognosis versus a good prognosis.

(D) The reply asserts that Ohira I is only providing background information conventional prognostic markers and that Ohira states that gene expression based systems can predict prognosis (p. 7 B2). The reply asserts that Ohira II teaches that when compared to other prognostic factors such as age, disease stage, and MYCN amplification microarray analysis showed the best sensitivity specificity balance and when combined with one or more prognostic factors accuracy can be further improved (p. 8 B2). The reply asserts that the claims do not exclude the use of other prognostic factors (p. 8 B2).

This has been fully reviewed but has not been found persuasive.

Although the claims do not exclude other prognostic factors, the instant specification has not provided guidance as to the predictable classification of subjects based upon 9 gene clustering when compared to all the prognostic type factors which effect such a classification. Herein in the instant case, the specification has not provided any example of taking a population and classifying that population based upon

the clustering effects for prognosis. Rather, the specification has provided a set of genes deduced from clustering analysis. As stated in argument C, such a set must be tested in a population to determine if other factors effect the classification. Such as in the case of Ohira II age, disease stage, and MYCN amplification would effect classification.

(E) The reply asserts that Ohira II reliably teaches the prediction of cancer patients tied to method reproducibility (p. 8 3a). The reply asserts that Ohira proposes a complete cross validation analysis and the accuracy of the microarray study (p. 9 3a) The reply asserts that these microarray studies for cancer outcome prognosis are at least 73% accurate and therefore show that expression studies are predictable (p. 9 3a).

This has been fully reviewed but has not been found persuasive. However, at issue here is if the microarray formed would be able to predictably prognosis a patient as having poor or good prognosis. , the American Heritage College dictionary defines prognosis as "a prediction of the probable course and outcome of a disease", "the likelihood of recovery from a disease"" or “a forecast or prediction”. In the instant case detecting and determining would be the same, with regard to the fact the skilled artisan would have to detect the expression levels and determine based on these expression levels rather the patient had good or poor prognosis. Herein in the instant case, the specification has not provided any guidance to determine the prediction, the

probable course and outcome of a disease, the likelihood of recovery, or a forecast or prediction of the disease in the patient. Rather, the working example in the specification provides correlations of expression levels at particular stages of disease, guidance has not been provided as to how to extrapolate these expression levels to the prediction the probable course and outcome of a disease, the likelihood of recovery, or a forecast or prediction of the disease in the patient. Herein in the instant case the specification has not shown that a population can be classified with prognosis based upon the 9 gene classifiers nor which genes need to be up or down regulated to be associated to a particular prognosis.

(F) The reply argues that validation studies of the analysis were performed using Mas5.0 software and RT PCR (p. 10-12 3b). The reply asserts that these 6 samples have been validated by cross validation techniques, RT PCR, and running 6 independent test samples on 5 different gene panels (p. 12 1st two paragraphs).

This has been fully reviewed but has not been found persuasive.

Shannon et al teaches that "putative relationships between clusters of genes and phenotypes need to be recognized as nothing more than hypotheses generated by clustering methods. The clustering process has not statistically validated the relationships and they must be formally validated through additional experiments. (p. 48 1st column last full paragraph of Shannon et al.). Herein in the instant case the

specification has not shown that a population can be classified with prognosis based upon the 9 gene classifiers nor which genes need to be up or down regulated to be associated to a particular prognosis. Therefore although the genes selected are cross validated, the specification has not provided a further validation experiment to determine if these 9 genes can be used to prognosis a patient.

(G) The reply asserts although the applicants' microarray data was validated by RT-PCR, the examiner uses Schramm to assert that the applicants work has not been replicated (p. 12 3rd paragraph). The reply asserts that Schramm indicates that there are severl genome wide mRNA expression profiling studies that have a reliable outcome fro neuroblastoma but with little or no overlap in the decision making genes (p. 13 2nd paragraph). The reply asserts that because the classifiers were different between Schramm and the instant invention a different set of decision making genes were selected (p. 13 3rd full paragraph). The reply asserts that Ein-Dor et al. identifies a similar phenomenon in sets of breast cancer survival related genes (p. 13 last parpahgra-14). Therefore based on Ein-Dor expression data form any set of patients would not result in the same 37 genes identified, but if these methods could be used to reliably determine good or poor prognosis as claimed for any neuroblastoma, Ein Dor indicates it could (p. 15 2nd papragrah-3rd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The reply seems to be asserting that the reason Schramm did not find that the 9 genes are associated with neuroblastama that depending on the clustering used

different sets of genes would be associated. This is persuasive based upon the amendments to the claims which limit the array to a particular set of genes. However, this set of genes have not been shown to reliable detect prognosis. Shannon et al teaches that "putative relationships between clusters of genes and phenotypes need to be recognized as nothing more than hypotheses generated by clustering methods. The clustering process has not statistically validated the relationships and they must be formally validated through additional experiments. (p. 48 1st column last full paragraph of Shannon et al.). Herein in the instant case, the instant specification has not provided any patient tested with the 9 genes and determining prognosis. Further, the claims do not indicate which genes should be up or down regulated to be correlated to poor or good prognosis.

(H) The reply asserts that based upon the nature of clustering analysis, the method will result in either good or poor prognosis regardless of the patient's age, tumor stage or expression level (p. 16 1st paragraph). The reply asserts that the question of operability because a question of utility (p. 16 2nd paragraph). The reply asserts that the office action has not made a rejection under 101 and has not provided a reasonable basis to support a conclusion that the claimed method is inoperable (p. 16 3rd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The MPEP clearly indicates that in some instances, the use will be provided, but the skilled artisan will not know how to affect that use (MPEP 2164.07 II). The MPEP

discloses that in such a case not rejection will be made under 35 USC 101, but rather a rejection under 35 USC 112, 1st paragraph will be made. Herein in the instant case the use is provided, however, as stated above, the skilled artisan will not know how to affect such a use. As pointed out in Mowry v. Whitney, 81 U.S. (14 Wall.) 620 (1871), an invention may in fact have great utility, i.e., may be "a highly useful invention," but the specification may still fail to "enable any person skilled in the art or science" to use the invention. 81 U.S. (14 Wall.) at 644.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday - Friday 9AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon

/Sarae Bausch/
Primary Examiner, Art Unit 1634